



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification³ : A61K 9/32, 9/52	A1	(11) International Publication Number: WO 83/ 00435 (43) International Publication Date: 17 February 1983 (17.02.83)
(21) International Application Number: PCT/GB82/00235 (22) International Filing Date: 28 July 1982 (28.07.82) (31) Priority Application Number: 8123573 (32) Priority Date: 31 July 1981 (31.07.81) (33) Priority Country: GB (71) Applicant (for all designated States except US): J.B TIL- LOTT LIMITED [GB/GB]; 25 Harley Street, London W1N 2BR (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : RHODES, John [GB/GB]; 25 Nantfawr Road, Cyncoed, Cardiff (GB). EVANS, Brian, Kenneth [GB/GB]; 9 Merevale, The Common, Dinas Powis, South Glamorgan (GB). (74) Agent: BURFORD, Anthony, Frederick; W.H. Beck, Greener & Co, 7 Stone Buildings, Lincoln's Inn, Lon- don WC2A 3SZ (GB).		(81) Designated States: AT (European patent), AU, BE (Eu- ropean patent), CH (European patent), DE (Euro- pean patent), DK, FI, FR (European patent), GB, JP, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i>
(54) Title: ORALLY ADMINISTRABLE PHARMACEUTICAL COMPOSITIONS (57) Abstract A solid dosage form, such as a capsule or tablet, containing a pharmacologically active agent is coated with an an- ionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7 but soluble in colonic intestinal juice, in a sufficient amount that the oral dosage form remains intact until it reaches the colon. The preferred anionic polymer is a partly methyl esterified methacrylic acid polymer in which the ratio of free carboxylic groups to ester groups is about 1 : 2. The invention has particular application to dosage forms of prednisolone and salts thereof, indomethacin, ibuprofen, and, especially, 5-amino-salicylic acid.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	KP	Democratic People's Republic of Korea
AU	Australia	LI	Liechtenstein
BE	Belgium	LK	Sri Lanka
BR	Brazil	LU	Luxembourg
CF	Central African Republic	MC	Monaco
CG	Congo	MG	Madagascar
CH	Switzerland	MW	Malawi
CM	Cameroon	NL	Netherlands
DE	Germany, Federal Republic of	NO	Norway
DK	Denmark	RO	Romania
FI	Finland	SE	Sweden
FR	France	SN	Senegal
GA	Gabon	SU	Soviet Union
GB	United Kingdom	TD	Chad
HU	Hungary	TG	Togo
JP	Japan	US	United States of America

ORALLY ADMINISTRABLE PHARMACEUTICAL COMPOSITIONS

The present invention relates to the administration of pharmacologically active agents to the large intestine and provides an orally administrable pharmaceutical composition for said purpose. It has particular, but not exclusive, application to the administration of 5-amino-salicylic acid (hereinafter referred to as 5-ASA) for the treatment of colonic or rectal disorders.

10 In the treatment of diseases or ailments of the colon or rectum administration of the pharmacologically active agent to the affected site may be required. Orally administrable pharmaceutical compositions however have frequently been found ineffective in this respect as a result of the absorption of the pharmacologically active agent in the digestive tract before the colon or rectum is reached. Consequently, the delivery of pharmacologically active agents to the colon or rectum has conventionally been achieved by 20 rectal administration, by the use of either suppositories or enemas. However, rectal administration generally is less convenient and less acceptable to a patient than oral administration. Further, said rectal administration is not suitable for treating the right side of the colon. In particular, suppositories



are only effective for the rectum and
enemas rarely reach beyond the left side of the colon.

Several "delayed release" forms of orally
administrable pharmaceuticals have been proposed. The
05 delayed release may result from the physical properties
of the pharmaceutical composition or from the chemical
and physical properties of a derivative of the active
ingredient. It is known to provide tablets and capsules
for oral administration with a coating which will
10 disintegrate to release the pharmacologically active
agent gradually when the tablet or capsule has reached
the acid environment of the stomach or the alkaline
environment of the small intestine. Similarly it is
known to provide tablets and capsules with a coating
15 permeable to the pharmacologically active agent
contained within and through which the agent is
gradually released.

It has been proposed in UK Patent Specification
No. 1219026 (published January 1971) to embed
20 individual particles of a pharmacologically active
agent in a slowly disintegrating or slowly dissolving
resin having a particular dissolution profile to
provide an orally administrable pharmaceutical
composition for selectively administering the agent to
25 the large intestine. The resin is selected such that
the agent remains substantially protected by the resin



while the particles travel through the stomach and small intestines of a patient and that the agent is substantially completely exposed at the time the particles reach the large intestine. In particular, the nature and amount of the resin is selected so that when a quantity of the embedded agent is introduced into a Stoll-Gershberg disintegration apparatus, submerged in a simulated intestinal fluid (made in accordance with the U.S. Pharmacopoeia, Volume XVII, 1965 at page 919 but modified by containing no pancreatin), and operated as described in the patent specification, 2% to 12% of the agent dissolves within an hour of the introduction of the agent into the fluid and 18% to 88% of the agent dissolves within three hours of said introduction. It is specifically stated that the resin is selected so that the dissolution rate of the agent is not pH dependent but is time dependent. The preferred resin is a high-viscosity grade modified vinyl acetate resin (available under the Registered Trade Mark "Gelva" C3-V30) and other specified resins are carboxylated polyvinyl acetates, polyvinyl/maleic anhydride copolymers, poly(methacrylic acid), ethylene/maleic anhydride copolymers, ethyl cellulose, methylacrylic acid/methyl methacrylate copolymers, waxes and mixtures thereof including mixtures with shellac. Tablets of the embedded particles coated with a standard coating



solution containing cellulose-acetate-phthalate are reported.

It will be appreciated that the carrier system disclosed in UK Patent Specification No. 1219026 relies upon the rate of disintegration or dissolution of the resin as the preparation passes through the gastro-intestinal tract. This time dependency makes it impossible to limit administration of the agent to the colon because of large variations in the transit time in the gastro-intestinal tract, especially in the stomach, which occur between different patients and in the same patient from time to time. It would appear that the carrier system has not been satisfactory in practice because we are not aware of any relevant product presently available in the UK or elsewhere and further we understand that the patent lapsed in 1979 by non-payment of renewal fees.

Anionic polymers have been known for many years to be of use in the preparation of coatings for tablets and other oral dosage forms to provide delayed or sustained release of the active agent. In particular, it has been known since at least 1974 to use for said coatings anionic copolymers of methacrylic acid and methacrylic acid methyl ester. Such a copolymer (available under the Registered Trade Mark "Eudragit" S) in which the ratio of free carboxyl groups to ester



groups is approximately 1:2 and having a mean molecular weight of 135,000 is known to be insoluble in gastric juice and poorly soluble in intestinal juice while an analogous copolymer (available under the Registered Trade Mark "Eudragit". L) differing only in so far as said ratio is approximately 1:1 also is insoluble in gastric juice but is readily soluble in intestinal juice. Said copolymers are usually employed to provide a coating of between about 25 and about 40 microns thick and the poorly soluble (in intestinal juice) copolymer usually is employed to reduce the dissolution (in intestinal juice) of the readily soluble copolymer. In general terms, anionic polymer coatings on oral dosage forms have been required to dissolve in aqueous medium at a pH below 7, usually between pH 5.5 and pH 7. Eudragit S dissolves above pH 7 but, as noted above, usually is employed in admixture with Eudragit L. As far as we are aware, said mixtures invariably dissolve below pH 7.

Salicylazosulphapyridine (also known as sulphasalazine or salazopyrin and hereinafter referred to as SASP) consists of sulphapyridine linked to a salicylate group by a diazo bond and has been found to be useful in the treatment of colitis, Crohn's disease, idiopathic proctitis and chronic arthritis. Orally administered SASP is only absorbed to a limited extent

before reaching the colon where azo-reductases produced by colonic bacteria act to split SASP into sulphapyridine and 5-amino-salicylic acid (i.e. 5-ASA).

Studies by A.K.A. Khan et al. (The Lancet, October 29 05 1977, p. 892) and others have shown the 5-ASA to be the pharmacologically active agent in the treatment of colonic and rectal ailments with SASP. Sulphasalezine appears merely to act as a chemical carrier to deliver 5-ASA to the colon and rectum. When administered orally 10 without the azo-bond joining them, sulphapyridine and 5-ASA are almost entirely absorbed from the small intestine before reaching the colon.

Several proposals have been made for the oral administration of 5-ASA avoiding using SASP in order to 15 reduce the occurrence of side effects attributable to the sulphapyridine moiety. For example, in US Patent Specification No. 4190716 (published February 1980), it was proposed to covalently bond the 5-ASA to a nonabsorbable pharmacologically acceptable organic 20 polymer backbone comprising a plurality of aromatic rings by azo bonds bridging aromatic carbon atoms and the 5-position carbon of 5-ASA.

In UK Patent Specification No. 2021409 (published December 1979), it was proposed that 5-ASA should be 25 administered concurrently or concomitantly with certain disodium cromoglycate-like compounds. Reference is made



to formulating 5-ASA in sustained or controlled release form by coating some or all 5-ASA particles or granules thereof with a slowly soluble or digestable or semi-permeable layer of material such as beeswax, Carnuba
05 wax, stearic or palmitic acids or cetyl alcohol.

Reference also is made to coating tablets of the coated or uncoated 5-ASA with a continuous film of a material such as shellac or cellulose acetate phthalate which is resistant and impermeable to gastric secretions but
10 susceptible to intestinal secretions. None of the coating materials specified or indicated in the specification are such as to prevent release of 5-ASA until the colon.

More recent proposals have been made in
15 International Patent Specification No. WD 81/02671 (published 1st October 1981) and European Patent Specification No. 40590A (published 25 November 1981), both of which specifications were published after the priority date of the present application. The
20 International Specification proposes formulating 5-ASA in a sustained release tablet or enterosoluble tablet form and specifies ethyl cellulose as the preferred coating material. No coating materials other than cellulose derivatives are mentioned and it is granules,
25 as distinct from tablets or other solid oral dosage forms, which are described as being coated.



The European Specification proposes coating a core of 5-ASA with a coating material comprising at least, (a) 10 to 85% by weight of an anionic carboxylic polymer soluble only above pH 5.5 and (b) 15 to 90% by weight of a water-soluble, quaternary ammonium substituted acrylic polymer. It is stated that the coating normally will be 3 to 60, preferably 10 to 30, microns thick and that partly methyl esterified methacrylic acid polymers are suitable anionic carboxylic polymers for use as component (a). In the Examples, Eudragit L and a mixture of Eudragit L and Eudragit S constitute the component (a) and in all cases the coatings dissolved at below pH 7. The coated bodies of the European Application are subsequently included in dosage units which normally contain at least 10 coated bodies. The rationale of the coating system is stated to be that the change of pH from acid to neutral at the pylorus triggers a change in the physical condition of the coating so that 5-ASA is subsequently released after a predetermined time lag by which time the preparation should have reached the colon. Although time of passage through the small intestine is relatively constant, it still varies from 2 to 5 hours and hence the carrier system does not provide for reliable release of 5-ASA only in the colon.



The Inventors have now found that 5-ASA reliably can be administered specifically to the large intestine, especially the colon, by simply coating a solid oral dosage form with a sufficient thickness of a partly methyl esterified methacrylic acid polymer which does not dissolve in aqueous medium below pH 7 but does dissolve below pH 7.5. This carrier system differs from those previously disclosed in relation to 5-ASA in that dissolution or disintegration does not occur until entry of the coated dosage form into the colon. In particular, there is substantially no leaching out of the 5-ASA downstream of the colon in the normal patient. Further, the system involves coating of the solid oral dosage form itself and not necessarily the coating of individual particles contained therein and hence the coated dosage form is relatively inexpensive and easy to manufacture. It is believed that the carrier system is entirely new in concept and of application to a wide range of pharmacologically active agents and anionic polymers.

According to a first aspect of the present invention, there is provided an orally administrable pharmaceutical composition for selectively administering a pharmacologically active agent to the large intestine comprising a solid oral dosage form containing said agent and coated with an anionic



polymer which is insoluble in gastric juice and in intestinal juice below pH 7 but soluble in colonic intestinal juice, for example below pH 7.5, said coating being sufficiently thick that the oral dosage
05 form remains intact until it reaches the colon.

According to a second aspect of the present invention, there is provided a process of preparing an orally administrable pharmaceutical composition for selectively administering a pharmacologically active
10 agent to the large intestine which comprises coating a solid oral dosage form containing said agent with an anionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7 but soluble in colonic intestinal juice, in a sufficient amount that
15 the oral dosage form remains intact until it reaches the colon.

According to a third aspect of the present invention, there is provided a method of treating colonic and rectal disorders which comprises
20 administering to a patient suffering such disorder a coated oral dosage form of the invention.

It is expected that any anionic polymer having the dissolution profile specified above can be used in the practice of the invention subject, of course, to
25 compatibility with the relevant active agent. However, presently preferred polymers are anionic carboxylic



polymers i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers in which the ratio of free carboxylic groups to ester groups is about 1:2 (i.e. Eudragit S). As previously stated, the anionic polymer should be insoluble in gastric juice and intestinal juice having a pH below 7. However, the polymer must dissolve in colonic intestinal juice, especially below pH 7.5, in order to make the active agent available in the large intestine, especially the colon.

15 The coating can, and usually will, contain a plasticiser and possibly other coating additives such as coloring agents, gloss producers, talc and/or magnesium stearate as well known in the coating art. In particular, anionic carboxylic acrylic polymers usually will contain 10 to 25% by weight of a plasticiser especially diethyl phthalate. Conventional coating techniques such as spray or pan coating are employed to apply the coating. (See for example D. Dreher "Film coatings on acrylic resin basis for dosage forms with controlled drug release" Pharma International 1/2 (1975) 3). As previously mentioned, the coating



thickness must be sufficient to ensure that the oral dosage form remains intact until the colon is reached. It has been found that a coating of between 60 and 150 microns usually is required. Preferably, the coating is
05 between 75 and 125 microns, especially between 80 and 100 microns. Obviously, a certain amount of trial-and-error experimentation will be required before ascertaining the optimum thickness of a particular polymer on a particular solid oral dosage form but such
10 experimentation is well within the capability of a man of average skill in the art.

The term "solid oral dosage form" means any non-liquid dosage form intended to be swallowed and having a sufficiently defined form to be coated.
15 Usually, the dosage form will be a conventional tablet or a capsule, e.g. a hard or soft gelatin capsule.

In addition to the pharmacologically active ingredient the oral dosage form may also contain one or more usual additives such as fillers (e.g. lactose or
20 dicalon phosphate), binders (e.g. starch or polyvinylpyrrolidone), lubricants (e.g. magnesium stearate, stearic acid or talc) and disintegrants (e.g. alginic acid, sodium starch glycolate or potato starch). The oral dosage forms may be prepared in conventional
25 manner.

As active agents in the composition of the



invention those compounds conventionally used in the treatment of colitis, ulcerative colitis, Crohn's disease, idiopathic proctitis and other diseases or disorders of the colon or rectum are of particular interest. Examples of active ingredients include 5-ASA; non-steroidal anti-inflammatory compounds, e.g. salicylates, indomethacin or ibuprofen; steroids, e.g. hydrocortisone, prednisolone, prednisolone phosphate, prednisolone metasulpho-benzoate sodium, prednisolone sodium phosphate, beclomethasone dipropionate and beclomethasone valerate; compounds active in the relief of constipation or diarrhoea, compounds active in the relief of spasm and in the improvement of motility, e.g. peppermint oil and other carminative essential oils; compounds for removal of excessive bile acids, e.g. cholestyramine; antibacterial or antiparasitic compounds, e.g. erythromycin, chloroquine, iodochlorhydroxyquin, disodohydroxyquin, neomycin and tetracyclines.

20 The invention has particular application to the administration of prednisolone or a salt thereof, indomethacin, ibuprofen and, especially, 5-ASA to the colon. In more general terms, the carrier system of the invention is particularly useful for the administration of active agents, especially topically active agents, to the right side of the colon which, as mentioned

previously, cannot reliably be reached with a rectally administered dosage form.

The pharmacologically active agents will be present in the oral dosage forms in suitable unit dosage amounts. Said amounts will be known or readily ascertainable by those skilled in the art. In many cases, said amounts are likely to be less than those presently administered by conventional delayed or sustained release dosage forms because of the high organ specificity of the dosage form of the present invention.

The following non-limiting Examples are provided to illustrate the compositions of the invention:-

Example I

A coating composition was prepared in the form of a lacquer containing the following ingredients:

EUDRAGIT S100		3g
Diethyl phthalate		0.75 ml
Silicone fluid DC 200/20CS		0.75 ml
20 Methanol	25 parts)	
	ad	100 ml
Dichloromethane	75 parts)	

A coating of 12mg/cm² dried lacquer substance (i.e. about 100 microns) was applied by spraying the above composition onto size No.1 hard gelatin capsules (Lok-Cap, Eli Lilly) each containing:-



- 15 -

5-ASA	400 mg
Lactose	46 mg
Polyvinylpyrrolidone	20 mg
Magnesium stearate	4 mg
05 Alginic acid	<u>10 mg</u>
Total	480 mg

Example II

The coating composition of Example I was applied to commercially available enterically coated tablets containing 5 mg prednisolone (Deltacortril Enteric Pfizer) to produce a coating of 12 mg/cm² dried lacquer substance (i.e. about 100 microns).

Example III

The coating composition of Example I was applied to size No. 1 hard gelatin capsules (Lok-Cap, Eli Lilly) containing:-

Indomethacin (active agent)	10 mg
Barium sulphate (radiopaque)	300 mg
Potato starch (disintegrant)	80 mg
20 Lactose (filler)	50 mg

to produce a coating.

The presence of barium sulphate was required in order to follow the progress of the capsules by radiographic techniques.

25

Example IV

Six convalescent patients, 3 male and 3 female



with a mean age of 57 years, from a general medical ward gave informed consent to a clinical trial. After breakfast they each swallowed six specially prepared capsules (No. 0 Lok-Cap Eli Lilly) coated with an acrylic based resin (Eudragit-S from Rohm Pharma GMBH) 120 microns in thickness applied by a modified air suspension technique (as described by Ekburg and Kallstand, *Svenk.Farm.Tidskr* 1972; 74; 375-78). The thickness of the coat was checked using a micrometer to establish the range of thickness and to measure both the wide and narrow end of the capsule. Each capsule contained barium sulphate (300 mg) potato starch (20 mg) and sulphapyridine (300 mg) as a convenient marker. Plain abdominal X-rays were taken at 5, 8 and 12 hours after ingestion and blood samples at 0, 3, 5, 7, 9, 12 and 24 hours after ingestion to assay sulphapyridine levels.

Sulphapyridine was analysed by high pressure liquid chromatography (HPLC) using a modification of the method described by Shaw et al (*J. Pharm. Pharmacol.* 1980;32;67). The analysis was performed on a LiChrosorb 10 RP 18 bonded silica reversed phase column (Merck). The mobile phase was acetonitrile - 0.05M potassium dihydrogen phosphate solution (20:80) containing 0.1 per cent tetrabutyl ammonium hydroxide. Sulphapyridine was detected spectrometrically at 260nm.



Serum samples were treated with an equal volume of ethanol to precipitate plasma proteins and after centrifugation, the supernatant was injected on to the chromatograph. Sulphapyridine concentration was read
05 directly from a calibration curve which was linear over the range 1-25 $\mu\text{g/ml}$ ($R = 0.99$).

X-rays showed that capsules remained intact in the stomach and proximal small bowel. In a few patients occasional capsules broke in the distal ileum (4 of 36)
10 but after 12 hours 32 capsules had reached the colon and of these, 23 had broken at this site. Serum levels of sulphapyridine showed a close correlation with radiographic findings. No drug was detected in any patient 3 hours after ingestion of the capsules and in
15 only 2 patients 5 hours after ingestion. Subsequent samples showed rising levels of sulphapyridine which corresponded with the radiological breakdown of capsules. Maximal levels were obtained at 12 or 24 hours after ingestion; the mean level at 12 hours was
20 8.3 $\mu\text{g/ml}$ and at 24 hours with 10.9 $\mu\text{g/ml}$.

The results show that with an acrylic based coating of Eudragit-S, 120 microns in thickness, capsules remained intact after oral ingestion until they reached the right side of the colon when the
25 capsule broke releasing its contents. The radiological evidence was particularly helpful since in most

instances one could identify the position of capsules within the intestine from soft tissue outlines. The complementary evidence from serum levels of sulphapyridine simply confirms the release and absorption of this marker corresponding with the radiological findings. Sulphapyridine is a useful marker because it is slowly cleared from the serum and one can demonstrate a rising level with progressive absorption from the colon. 5-ASA was not used as a marker because it is relatively poorly absorbed and excreted rapidly after acetylation so that serum levels are very low.

Example V

Seventy-two patients who were in remission with ulcerative colitis or proctitis and taking at least 4 sulphasalazine tablets each day gave their informed consent to a clinical trial. Remission was defined as the passage of three or fewer stools each day without blood or slime during the previous month. Thirty-six patients were male and 36 female. Sigmoidoscopy with rectal biopsy was performed initially and patients only entered the trial if the mucosa was normal (grade 1) or oedematous (grade 2). Biopsies were coded and reviewed by a pathologist who graded them as 1 (normal) or grades 2, 3 or 4 representing mild, moderate or severe inflammatory change.

Patients completed diary cards throughout 16 weeks



- 19 -

and were asked to note any side effects; they were seen after 4, 12 and 16 weeks. On completion of the trial a further sigmoidoscopy was performed to ensure the mucosa appeared normal. Patients were seen promptly if
05 symptoms recurred and a sigmoidoscopy was performed at that time. A relapse was defined as a recurrence of symptoms with increased stool frequency and blood loss with sigmoidoscopic changes of contact or spontaneous mucosal haemorrhage (grade 3) or the presence of pus
10 with bleeding and ulceration (grade 4).

Blood was taken for a routine blood count and examination of the film at each clinic attendance and measurements of the serum electrolytes and liver function tests were performed initially and after 16
15 weeks.

The study, which was randomised and double-blind in design, involved using identical placebo tablets for both sulphasalazine and 5-ASA; each patient was given two sets of tablets with either active 5-ASA and
20 placebo sulphasalazine or placebo 5-ASA and active sulphasalazine. The patient's usual dose of sulphasalazine was continued with a minimum dose of 2 grams daily. The tablets of 5-ASA contained 400 mg (ie the amount of 5-ASA contained in 1 gram of sulphasalazine).
25 At least 3 tablets of 5-ASA were taken daily (1200 mg) with an increased dose of 1 tablet for each gram of



sulphasalazine above the minimum entry dose of 2 grams for patients taking a high dose of sulphasalazine.

Compliance was checked at each hospital visit by counting the number of tablets returned. 5-ASA powder
05 was obtained from Aldrich Chemicals and the tablets were coated by Rohm Pharma GHB using the modified method of Eckberg and Kallstrand 1972 (supra) with an acrylic-based resin (Eudragit-S) with a thickness between 100-130 microns.

10 Five of the 72 patients were withdrawn from the study; 4 female and 1 male because of pregnancy in 2 females and constipation in a third. A further 2 patients failed to take the medicine regularly. Of the remaining 67 patients, 15 relapsed and 52 completed the
15 trial. Details of the two groups are in Table 1. Nine patients relapsed on 5-ASA and 6 on sulphasalazine; this difference is not statistically significant (chi squared).

Sixteen patients reported side effects of
20 headache, nausea or indigestion on two or more monthly diary cards during the trial period but there was no difference between the 5-ASA and sulphasalazine group. There was no significant changes identified in either the haematological or biochemical parameters which were
25 measured.

Satisfactory biopsies from 61 patients confirmed



- 21 -

the absence of inflammation in most patients (51 of 61 patients). Four showed grade 2 inflammation and 6 grade 3. Three patients did not have a biopsy and in 3 others it proved unsatisfactory.

05 This double-blind study shows that 5-ASA tablets (400 mg) coated with an acrylic-based resin (Eudragit-S) which was between 100 and 130 microns in thickness is as effective as sulphasalazine in maintaining remission in colitis. The trial which involved 72
10 patients followed relapses over 16 weeks and since previous studies have shown the majority of relapses occur within the first 12 weeks we feel that the design is adequate to demonstrate whether the alternative preparation is as effective as sulphasalazine during
15 this period.

 This preparation represents an important advance in the management of patients with colitis since it may be given to those patients who are unable to take sulphasalazine because of allergic or other adverse
20 reactions. Male infertility is also likely to be due to the sulphapyridine component. Greater doses of 5-ASA can be given because of its low toxicity and these may prove to be more effective therapeutically.



Table 1

Details of 67 patients treated with 5-amino salicylic acid or sulphasalazine during 16-week trial.

<u>PATIENTS</u>		<u>5-ASA</u>		<u>SLP</u>	
05	Number	34		33	
	Sex M/F	14	20	21	12
	Age \pm SD	44.9 \pm 15.3		50.2 \pm 15.6	
	Duration of disease \pm SD	7.2 \pm 5.5		9.3 \pm 6.4	
10	Time since last attack	1.6 \pm 1.4		2.1 \pm 2.3	
<u>Extent of Disease:</u>					
	Proctitis	17		19	
	Left sided	13		5	
20	Extensive	4		9	
	Relapses	9		6	

(p = NS)



Example VI

Tablets were manufactured to the following

formula:-

	<u>Placebo</u>		<u>Active</u>	
05	Emcompress	714mg	5-ASA	400mg
	Mag. Stearate	8mg	Barium Sulphate	25mg
	Barium Sulphate	25mg	Lactose	125mg
	Burnt Umber	6.1mg	Polyvinylpyrrolidone	6mg
	Explotab	<u>19mg</u>	Magnesium Stearate	11.8mg
10		727mg	Talc	11.5mg
			Explotab	<u>15.7mg</u>
				595mg

Matching active and placebo tablets were formulated and produced.

- 15 The tablets were coated with the coating solution of Example 1 to provide a thickness of about 120 microns. The rotational speed of the tablets in the coating apparatus was reduced to a minimum in order to reduce the shear. The coating solution during the
- 20 initial stage was sprayed on to the tablets at as high a rate as possible. Coated active and placebo tablets were examined as follows:-

Placebo

- (a) Disintegration completed in 6hrs. 20 minutes.
- 25 (b) pH of buffer before commencing = 7.21
- (c) pH of buffer after test = 7.16



Active

(a) Disintegration incomplete after 6hrs. 36 minutes.

(b) pH of buffer before commencing = 7.16

(c) pH of buffer after test = 6.549

05 Control

Buffer solution at pH = 7.21. The pH of the buffer solution was checked as follows:

<u>Time</u>	<u>pH</u>
0	7.21
10 15 mins.	7.197
30 mins.	7.189
1 hr.	7.189
2hrs.	7.185
3hrs.	7.182
15 5hrs. 44 mins.	7.181
24hrs.	7.195

Radiological examination of the coated tablets in patients indicated that their degree of radio-opacity was lower than expected. This could cause problems when
20 a tablet becomes superimposed over another radio-opaque area and therefore it was decided to drill out the centre of one hundred tablets, fill the cavity with BaSO₄ powder and re-seal with Eudragit-S coating.

Studies in patients showed that the tablets were
25 easily visible and disintegration commenced in the ascending colon.



CLAIMS

1. An orally administrable pharmaceutical composition for selectively administering a pharmacologically active agent to the large intestine comprising a solid
05 oral dosage form containing said agent and coated with an anionic polymer which is insoluble in gastric juice and in intestinal juice below pH 7 but soluble in colonic intestinal juice, said coating being sufficiently thick that the oral dosage form remains
10 intact until it reaches the colon.
2. A composition as claimed in Claim 1 wherein the anionic polymer is an anionic carboxylic acrylic polymer.
3. A composition as claimed in Claim 2 wherein the
15 anionic polymer is a partly methyl esterified methacrylic acid polymer.
4. A composition as claimed in Claim 1 wherein the coating is 75 to 125 microns thick.
5. A composition as claimed in Claim 4 wherein the
20 coating is 80 to 100 microns thick.
6. A composition as claimed in Claim 1 wherein the oral dosage form is a tablet.
7. A composition as claimed in Claim 1 wherein the oral dosage form is a capsule.
- 25 8. A composition as claimed in Claim 1 wherein the pharmacologically active agent is 5-amino-salicylic



acid or a pharmaceutically acceptable salt or ester thereof.

9. A composition as claimed in Claim 1 wherein the pharmacologically acceptable agent is prednisolone or a salt thereof, indomethacin, or ibuprofen.

10. An orally administrable pharmaceutical composition for selectively administering 5-amino-salicylic acid or a pharmaceutically acceptable salt or ester thereof to the large intestine comprising a capsule or tablet containing said agent and coated with a 60 to 150 microns thick layer of a partly methyl esterified methacrylic acid polymer in which the ratio of free carboxyl groups to ester groups is about 1:2, whereby the capsule or tablet remains intact until it reaches the colon.

11. A process of preparing an orally administrable pharmaceutical composition for selectively administering a pharmacologically active agent to the large intestine which comprises coating a solid oral dosage form containing said agent with an anionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7 but soluble in colonic intestinal juice, in a sufficient amount that the oral dosage form remains intact until it reaches the colon.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 82/00235

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ¹		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ³ : A 61 K 9/32; A 61 K 9/52		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
IPC ³	A 61 K 9/00; A 61 K 31/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X,Y	Manufacturing Chemist & Aerosol News, vol. 44, no. 6, June 1973, Morgan-Grampian Ltd. (London, GB) K. Lehmann: "Acrylic coatings in controlled release tablet manufacture", pages 39-41, see page 40 column 1, line 11 - column 2, line 2; page 41, column 1, last paragraph - column 2, first paragraph	1-11
Y	US, A, 3784683 (PRILLIG et al.) 8 January 1974 see the entire document & GB, A, 1219026 (ABOTT) 13 January 1971 (cited in the application)	1-11
Y	GB, A, 2021409 (FISONS LTD.) 5 December 1979 see page 1, lines 121-127; page 4, lines 38-67. (cited in the application)	1-8, 10, 11
Y	The Merck Index, 8th edition, 1968; Merck & Co. (Rahway, US), see page 560 "Ibuprofen"; page 566 "Indomethacin";	9 ./.
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²		Date of Mailing of this International Search Report ²⁰
4th November 1982		24th November 1982
International Searching Authority ¹		Signature of Authorized Officer ²⁰
EUROPEAN PATENT OFFICE		G.L.M. Krueger

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
	pages 861,862 "Prednisolone"	
Y	<p>--- R. Voigt: "Lehrbuch der Pharmazeutischen Technologie", 1973, VEB Verlag Volk und Gesundheit (Berlin, DD) see pages 213-218, in particular page 214, second but last paragraph</p> <p>---</p>	1-7
A	<p>--- Hagers Handbuch der Pharmazeutischen Praxis vol. 7, part B, 1977, Springer Verlag, (Berlin, DE), see pages 401-403, "Endragit"</p> <p>---</p>	
A	<p>--- GB, A, 1017674 (HOFFMANN-LA ROCHE) 19 January 1966 see the entire document</p> <p>---</p>	
P,A	<p>--- Chemical Abstracts, vol. 95, no. 14, 5 October 1981 (Columbus, Ohio, US) B.M. Cordoba et al.: "Diffusion of novocaine in enteric-coated tablets. Part 2.", see page 360, column 2, abstract no. 121042k, Farm. Nueva 1980 46(524), 511-16,521-5</p> <p>-----</p>	